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Onset, Progression, and Plateau of Skeletal Lesions in Fibrous Dysplasia and the Relationship to Functional Outcome

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ABSTRACT: Most lesions in FD and their attendant functional disability occur within the first decade; 90% of lesions are present by 15 years, and the median age when assistive devices are needed is 7 years. These findings have implications for prognosis and determining the timing and type of therapy.

Introduction: Fibrous dysplasia of bone (FD) is an uncommon skeletal disorder in which normal bone is replaced by abnormal fibro-osseous tissue. Variable amounts of skeletal involvement and disability occur. The age at which lesions are established, the pace at which the disease progresses, if (or when) the disease plateaus, and how these parameters relate to the onset of disability are unknown. To answer these questions, we performed a retrospective analysis of a group of subjects with FD.
Materials and Methods: One hundred nine subjects with a spectrum of FD were studied for up to 32 years. Disease progression was assessed in serial ^{99}Tc-MDP bone scans by determining the location and extent of FD lesions using a validated bone scan scoring tool. Physical function and the need for ambulatory aids were assessed.
Results: Ninety percent of the total body disease skeletal burden was established by age 15. Disease was established in a region-specific pattern; in the craniofacial region, 90% of the lesions were present by 3.4 yr, in the extremities, 90% were present by 13.7 yr, and in the axial skeleton, 90% were present by 15.5 yr. Twenty-five of 103 subjects eventually needed ambulatory aids. The median age at which assistance was needed was 7 yr (range, 1–43 yr). The median bone scan score for subjects needing assistance was 64.3 (range, 18.6–75) compared with 23.1 (range, 0.5–63.5) in the unassisted subjects ($p < 0.0001$). Among subjects needing assistance with ambulation, 92% showed this need by 17 yr.
Conclusions: The majority of skeletal lesions and the associated functional disability occur within the first decade of life. The implication is that the window of time for preventative therapies is narrow. Likewise, therapeutic interventions must be tailored to where the patient is in the natural history of the disease (i.e., progressive disease [young] versus established disease [older subjects]). These findings have implications for prognosis, the timing and type of therapy, and the development of trials of new therapies and their interpretation.
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Key words: fibrous dysplasia, bone, outcomes, McCune-Albright syndrome, *GNAS*, $G_s\alpha$

INTRODUCTION

Fibrous dysplasia of bone (FD) is a skeletal disorder characterized by replacement of normal bone and bone marrow with abnormal fibro-osseous tissue.[1,2] It was first defined by Lichtenstein in 1938, and further categorized in 1942 by Lichtenstein and Jaffe.[3] The actual incidence and prevalence of FD are difficult to estimate, but it may represent as many as 7% of benign bone tumors.[4] FD results from a block in the differentiation of the primitive bone marrow stromal cells (sometimes referred to as mesenchymal stem cells) to mature bone cells (osteoblasts and osteocytes).[5,6] FD may occur as an isolated condition or as part of the McCune-Albright syndrome (MAS), which is characterized by at least two of the following triad: polyostotic FD, café-au-lait spots, and hyperfunctioning endocrinopathies.[6–9] The most common endocrinopathies are precocious puberty, hyperthyroidism, growth hormone excess,

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TABLE 1. DEMOGRAPHIC DATA ON SUBJECTS INCLUDED IN DISEASE PROGRESSION AND FUNCTIONAL ANALYSES

	Progression analysis		*Functional analysis*	
Category	*Included patients (n = 66)*	*Excluded patients (n = 43)*	*Included patients (n = 103)*	*Excluded patients (n = 6)*
Sex (F/M)	39/27 (59.1%/40.9%)	27/16 (62.8%/37.2%)	64/39 (62.1%/37.9%)	2/4 (33.3%/66.6%)
Diagnosis (MAS/PFD/MFD)	52/11/3 (78.8%/16.7%/4.5%)	37/4/2 (86%/9.3%/4.7%)	84/14/5 (81.5%/13.6%/4.9%)	5/1/0 (83.3%/16.7%/0%)
Any endocrinopathy (y/n)	43/23 (65.2%/34.8%)	26/17 (60.5%/39.5%)	70/33 (64%/36%)	3/3 (50%/50%)
Precocious puberty (y/n)	36/30 (54.5%/45.5%)	17/26 (39.5%/60.5%)	52/51 (50.5%/49.5%)	1/5 (16.7%/83.3%)
Hyperthyroid (y/n)	18/48 (27.3%/72.7%)	12/31 (27.9%/72.1%)	29/74 (28.2%/71.8%)	1/5 (16.7%/83.3%)
Hyperparathyroid (y/n)	8/58 (12.1%/87.9%)	3/40 (7.0%/9.0%)	11/92 (10.7%/89.3%)	0/6 (0%/100%
Growth hormone excess (y/n)	14/52 (21.2%/78.8%)	5/38 (11.6%/88.4%)	17/86 (16.5%/83.5%)	2/4 (33.3%/66.7%)
Cushings syndrome (y/n)	4/62 (6.1%/93.9%)	1/42 (2.3%/97.7%)	5/98 (4.9%/95.1%)	0/6 (0%/100%)
Phosphate wasting (y/n)	27/39 (40.9%/59.1%)	11/32 (25.6%/74.4%)	38/65 (36.9%/63.1%)	0/6 (0%/100%)
Median bone scan score	37.6 (range, 1.8–75)	24.8 (range, 0.5–75)	33 (range, 0.5–75)	NA
Median age at first bone scan	19 (range, 1–57)	NA	NA	NA
Median age at final bone scan	23.1 (range, 6.4–69.9)	NA	20 (range, 3–84)	NA
Median age at follow-up	23.2 (range, 6.4–60.7)	19.1 (range, 3.3–84)	22 (range, 3–84)	11 (range, 7–43)

y, yes; n, no; NA, not applicable.

and Cushing's syndrome,[10] and a significant proportion of the patients have renal phosphate wasting.[11]

The molecular etiology of FD and MAS is activating mutations of the cAMP-regulating protein, $G_s\alpha$.[12,13] The lack of vertical transmission, along with the observation that skin and bone lesions, tend to lateralize and respect the midline helped to establish that the disease is the result of postzygotic mutations, and thus, patients are somatic mosaics.[14] The time and location of the occurrence of the mutation during embryonic development dictates the phenotype.[15] One consequence of this is a wide spectrum of disease severity. Skeletal disease commonly leads to bone pain, fragility, fractures, and an adverse effect on health-related quality of life.[16–18] In a minority of patients, frank physical disability occurs and leads to a spectrum of disability, from walking with aids, such as a cane or walker, to the need for a wheelchair.

The age at which skeletal lesions initially manifest, the pace at which they progress, and the age at which maximum skeletal burden is reached are not known. In addition, which patients are at risk for disability, the extent of skeletal involvement (skeletal disease burden) that leads to disability, and the age of onset of disability are also unknown. To answer these questions, we performed a retrospective analysis of a heterogeneous group of subjects with FD using a validated quantitative bone scoring tool that measures skeletal disease burden.

MATERIALS AND METHODS

Subjects

One hundred nine subjects with FD were evaluated at the NIH over 32 yr, between 1973 and 2006. All subjects or parents gave informed consent and were enrolled in Institution Review Board–approved studies. The diagnosis of FD was confirmed by clinical history, physical exam, radiographic findings, histopathology, and when necessary, gene mutation analysis. All subjects underwent endocrine and metabolic evaluation for evidence of MAS using standard commercial assays. Subjects who had at least two ^{99}Tc-MDP bone scans that were at least 8 mo apart were included in the analysis of skeletal disease progression. Sixty-six of the 109 subjects met this inclusion criterion. Demographic characteristics of subjects included and excluded from the progression and functional analyses are shown in Table 1. To be included in the functional analysis, subjects had to have had one bone scan and information on ambulatory status. One hundred three subjects met the criteria for functional analysis. Five were excluded because they did not have bone scans, and in one patient, current functional status was not available.

Bone scans

One hundred four subjects had at least one standard ^{99}Tc-MDP bone scan. A total of 266 bone scans (in 66 subjects) were scored for the progression analysis, and 103 bone scans (in 103 subjects) were scored for the functional

analysis. For the functional analysis, the most recent bone scan was used. All bone scans were scored by two individuals using a previously validated skeletal scoring instrument.[19] A description of the bone scan scoring tool follows: briefly, the skeleton was divided into 11 anatomical segments, and FD lesions were noted as areas of tracer uptake. The percent of that anatomical segment that was involved with FD was estimated and multiplied by the estimated percentage of the entire skeleton for each of the 11 segments. The bone scan score equals the sum of the numbers from the 11 segments. No skeletal disease yields a score of zero, and total skeletal involvement (panostotic disease) yields a score of 75. Measurement of skeletal disease burden with this tool has been shown to correlate with markers of bone turnover,[19] serum fibroblast growth factor (FGF)-23 and tubular reabsorption of phosphate,[20] and health-related quality of life.[17] All sites detected on bone scan that were scored as FD were confirmed as such by review of radiographs (and when available, relevant CT or MRI scans). For the purpose of correlating bone scan scores with functional status, not only was the total skeleton bone scan score analyzed, but analyses of three subregions were also performed (lower extremity + spine + pelvis, lower extremity + pelvis, and lower extremity only).

Disease progression

In an effort to determine the onset, progression, and plateau of FD, we measured the change in skeletal disease in individuals over time. The change in the bone scan score from one scan to the next in each individual was measured. To be able to compare the changes between subjects with different amounts of FD, the severity of FD between subjects was normalized by establishing each subject's final bone scan score as 100% of that individual's disease and the changes between scans as a percent of the final. To be assured that a scan represented what was likely to be the "final" score, only subjects whose final bone scan was performed after the age of 15 were studied. Fifteen was established as the minimum age for the final score after the data were modeled using various age cut-offs and it was determined that it was the lowest age after which there were negligible increases in the bone scan score for the group as a whole. In addition, subjects with very low bone scan scores (<10, primarily older patients with monostotic FD) were excluded from the analysis. This was done to eliminate the data being biased by clinically insignificant, very small changes in skeletal burden that would be scored as large percent changes. Thus, the changes in bone scan score were calculated on 266 scans from $N = 66$ subjects, and 172 pairwise comparisons were made. The disease progression data were best-fitted to a cubic regression model.

New FD lesions

In an effort to determine whether there was a pattern to when and where new FD lesions occurred, serial scans from subjects were analyzed, and the location of a new lesion and the age range during which the new FD lesion appeared were recorded. New bone scan lesions were confirmed to be FD by review of radiographs, CT, or both.

Functional status

Subjects' medical records were reviewed to determine the age of onset of ambulatory disability. Ambulatory disability was defined as use of a crutch, cane, walker, or wheelchair during the majority of the day. Temporary use of assistance devices after fractures and surgeries was not included.

Statistical analysis

Regression equations were used to determine the age at which 50%, 75%, and 90% of the lesions for the total body and subregions (craniofacial, axial, and extremities) were present. Neither linear nor logarithmic regressions of age were sufficient to model the changes in lesions. The disease progression data were ultimately fitted to a cubic regression curve to model the percentage of total and regional bone scan scores. For the analysis of functional status, groups were compared using the Mann-Whitney U test. $p < 0.05$ was considered statistically significant. All analyses were performed using SAS (version 8.2; SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

Sixty-six subjects met the inclusion criteria for the progression analysis. This included 39 females and 27 males. Fifty-two subjects had MAS, 11 had polyastotic FD (PFD), and 3 had monostotic FD (MFD). Forty-three subjects had at least one endocrinopathy. The most common was precocious puberty, affecting 43 subjects. Cushing's syndrome was the least prevalent, which only affected four subjects—all during the neonatal period. One hundred three subjects met the inclusion criteria for the functional analysis. This included 64 females and 39 males. Eighty-four subjects had MAS, 14 had PFD, and 5 had MFD. Seventy subjects had at least one endocrinopathy, with precocious puberty being the most common, affecting 52 subjects. Cushing's syndrome was the least prevalent, which only affected five subjects—all in the neonatal period. Patient characteristics are summarized in Table 1.

Progression of skeletal disease

The 266 total body bone scan scores for all 66 subjects with at least two bone scans performed >8 mo apart are shown in Fig. 1. When displayed in this fashion, it is clear that the population included patients with a spectrum of disease burden, from very mild disease to severe disease involving the entire skeleton. In addition, it is apparent there is very little change in an individual's bone scan score beyond the age of 15 yr.

To assess disease progression and the plateau of FD lesions over time, the percent change in the bone scan score, relative to the final bone scan score for each individual, was calculated and fitted to a cubic regression equation. This was calculated for the total body, the craniofacial and axial skeleton, and the extremities. The percent change in bone scan score could be calculated for 266 bone scans based on $N = 66$ subjects and 172 comparisons. The curve and equation for the total body are shown in Fig. 2, and the equa-

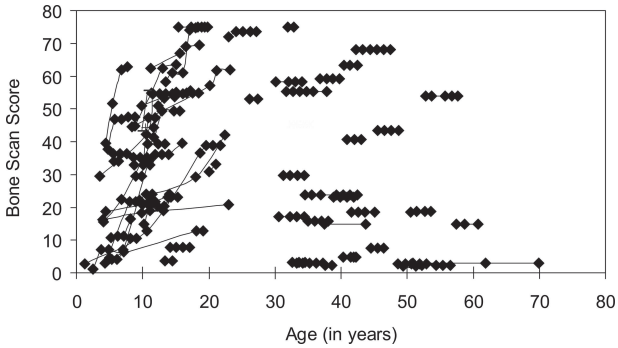

FIG. 1. All bone scan scores in all subjects. Each total body bone scan score for each subject is shown. Evident is the fact that a group of subjects with a broad spectrum of disease were studied, that significant changes in bone scan scores were more likely to occur at an early age, and that there was very little change later in life.

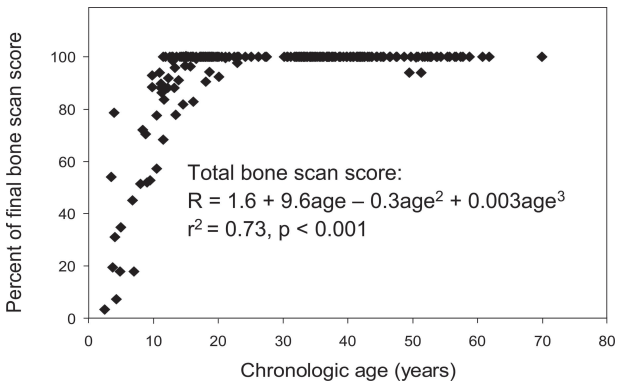

FIG. 2. Disease progression in FD. Each subject's final total body bone scan score was established as representing 100% of that subject's disease, and the change in scores from one scan to the next, expressed as percent of the final, are displayed. The data were fitted to a cubic regression curve and the equation displayed ($N = 66$ subjects, 266 scans).

tions for the curves of all the skeletal regions are provided in Table 2. By these calculations, craniofacial disease was established the earliest, followed by bones in the extremities, and the axial skeleton. However, the craniofacial regression model was barely significant ($p = 0.03$) and may not be as reliable as the equations for the other segments. Regression analyses of these data were used to calculate the ages at which 50%, 75%, and 90% of the disease was established in the total skeleton, craniofacial, axial, and appendicular skeleton, respectively (Table 3). We estimated that 90% of the total body disease was established by 15 yr of age, 90% of craniofacial disease by the age of 3.4 yr, and that in the axial skeleton and extremities, the ages at which 90% of the disease was established were 15.5 and 13.7 yr, respectively. Pairwise comparison of the curves for the rate of change in FD lesions in the various anatomical regions confirmed that the ages at which disease is established in the craniofacial skeleton, axial skeleton, and extremities is significantly different (Table 4). However, there was no difference between the total body and the extremities.

TABLE 2. CUBIC REGRESSION ANALYSIS EQUATION BY REGION

Region	*Equation*	r^2	*p*
Total body	$R = 1.6 + 9.6age - 0.3age^2 + 0.003age^3$	0.73	<0.001
Craniofacial	$R = 86.3 + 1.1age - 0.03age^2 + 0.0002age^3$	0.08	0.03
Axial	$R = 25.6 + 12.3age - 0.4age^2 + 0.003age^3$	0.73	<0.001
Extremities	$R = 13.8 + 8.7age - 0.3age^2 + 0.002age^3$	0.64	<0.001

The change in bone scan scores were calculated on 266 bone scans, $N = 66$ subjects.

TABLE 3. AGE AT WHICH LESIONS ARE ESTABLISHED BY SITE

Percent of lesions present	*Craniofacial*	*Axial*	*Extremity*	*Total body*
50%	NA	7.4	4.9	5.7
75%	NA	11.7	9.6	10.7
90%	3.4	15.5	13.7	15

NA, not applicable.

TABLE 4. PAIRWISE COMPARISON

Comparison of bone scan scores	*p*
Total body vs. craniofacial	<0.01
Total body vs. axial	<0.01
Total body vs. extremity	NS
Axial vs. craniofacial	<0.01
Axial vs. extremity	<0.01

NS, not significant.

New FD lesions

The anatomical location and age range during which new FD lesions occurred are shown in Table 5. Eighty-nine new confirmed FD lesions were identified. More than one half of the new lesions (52%) occurred before the age of 10, and only 18% occurred after the age of 20. Fifty-one percent of the new lesions occurred in the axial skeleton, 47% in the extremities, and only 2% in the craniofacial region.

Functional status, skeletal disease burden, and ambulatory status

The amount of skeletal disease was significantly higher among subjects needing assistance with ambulation. The mean total bone scan score of subjects needing any assistance with ambulation versus those who did not was 60.2 ± 14.8 versus 24.4 ± 18.6 ($p < 0.0001$, Mann-Whitney *U* test; median, 68.8 versus 19.2; Fig. 3A), but there was no significant difference between the bone scan scores of subjects using wheelchairs and subjects using "any" assistance device. Similar results were found in analyzing the legs + pelvis + spine subregion (36.3 ± 8.0 versus 14.9 ± 12.1; $p < 0.0001$; Fig. 3B), as well as the legs + pelvis (32.0 ± 6.5 versus 13.8 ± 11.6; $p < 0.0001$) and legs alone (28.2 ± 5.7 versus 12.1 ± 11.0; $p < 0.0001$).

Table 5. Site, Number, and Location of the Appearance of New FD Lesions

Bone(s)	*No. of new lesions*	*<10 yr*	*<15 yr*	*<20 yr*	*<25 yr*	*>25 yr*
Skull	1	1	0	0	0	0
Mandible	1	1	0	0	0	0
Scapula	3	2	1	0	0	0
Femur	3	2	—	1	0	0
Tibia	3	2	1	0	0	0
Humerus	6	2	2	1	1	0
Radius	6	6	0	0	0	0
Ulna	7	4	2	—	1	0
Pelvis	7	5	2	0	0	0
Hand	8	4	4	0	0	0
Fibula	9	2	3	2	2	0
Sternum	11	2	5	1	—	2
Ribs	11	6	2	1	—	2
Spine						
Cervical = 3		1	1	1	0	0
Thoracic = 3		1	1	1	0	0
Lumbar = 7	13	4	3	0	0	0
Totals	89	46	27	8	4	4

Twenty-five of 103 subjects (24%) needed ambulatory assistance with a cane, crutch, crutches, walker, or wheelchair. The age at which the need for assistance with ambulation occurred is summarized in Table 6. The median age at which subjects needed assistance with ambulation was 7 yr (mean, 9.6 ± 9.0 yr; range, 1–43 yr). Seventeen subjects eventually needed a wheelchair at a median age of 8.0 yr (mean, 8.4 ± 6.0 yr; range, 2–27 yr). The age of use of any ambulation device and the use of a wheelchair did not differ significantly ($p > 0.8$, Mann-Whitney U test). Most of the subjects (13/25) either needed no assistance device before using a wheelchair or used a device for <1 yr before needing a wheelchair.

DISCUSSION

These data address several important questions in the study and treatment of FD: when do FD lesions appear and progress; when does the appearance and growth of FD lesions cease; are there differences between the various skeletal segments as to when FD appears, progresses, and progression ceases; and what degree of FD skeletal disease burden is associated with impaired ambulation; at what age is ambulation likely to become impaired? These data showed that using the sensitive tool of isotopic bone scanning, FD lesions begin to appear at a young age, particularly in the craniofacial region, and that >90% of FD lesions are established at all sites before the age of 15 yr. One implication of this finding is that measures to "prevent" FD or its "spread," and trials to test such interventions, must be instituted at a very early age. Furthermore, results of past and future studies that assess the impact of a therapeutic intervention on prevention, spread, and functional outcome will need to be interpreted in the context of these natural history findings. That is, stable disease or function in older subjects may reflect the natural history of the disease and not the effect of an intervention.

Somewhat surprising was the very early age by which craniofacial skeletal disease was established. This difference between the craniofacial region and other regions may be related to the fact that the craniofacial skeleton is a tissue derived from neuroectoderm, as opposed to the rest of the skeleton, which is of mesodermal tissue. Or it may be that, relative to the rest of the skeleton, the skull grows less in size in the postnatal period. For reasons that remain to be elucidated, craniofacial FD lesions differ significantly from other skeletal sites. It has been shown that bone marrow stromal cells derived from craniofacial structures are different from such cells found elsewhere, and this finding may be a reflection of that.[21,22] One manifestation of the differences between craniofacial FD and axial/appendicular disease is the profound effect of growth hormone (GH) excess on craniofacial FD, leading sometimes to massive macrocephaly and vision and hearing loss.[23–25] The finding of very early disease establishment in the craniofacial region, together with increased morbidity associated with GH excess, emphasizes the need for very early screening and treatment of GH excess.

Perhaps one of the most pressing issues facing clinicians, patients, and the parents of patients with FD is the effect of FD on ambulation. Impact on ambulation is the single most important determinant of health-related quality of life in FD.[17] Many patients and parents live with a fear that they or their children will end up disabled. The ability to determine the skeletal disease burden associated with impaired ambulation and the age of onset of disability is an important contribution to patients and clinicians. These data indicated that onset of disability occurs relatively early and is usually associated with a high disease burden. Combine these points with the fact that 75% of the disease is established by the age of 10 yr, and in many cases, clinicians will be able to provide assurance to parents that their child will be spared from significant functional disability. These findings are useful for providing prognostic advice to patients and their families as well as informing/influencing decisions about therapeutics and timing of interventions.

It is of interest to note lower extremity bone scan scores were not better than the total body score in terms of discriminating those subjects needing assistance with ambulation from those who did not. Because disease in the lower extremities is the major factor in determining such disability, one may have anticipated lower extremity scores would have been more discriminate in separated patients needing assistance from those who did not. This may reflect that fact that the degree of renal phosphate wasting correlates with the skeletal disease burden[20] and that patients with greater total body burden are more likely to have more renal phosphate wasting and hypophosphatemia and thus are more likely to have FD lesional osteomalacia.[5,26]

Taken together, these data begin to provide a clearer picture of the natural history of FD. The data point to the fact that the majority of FD lesions are established at a young age, especially in the craniofacial region, and that stabilization of FD occurs roughly after the age of 15 yr. If disability is going to occur, it usually occurs when there is very significant disease burden present, and in most cases will occur by age 7 yr.

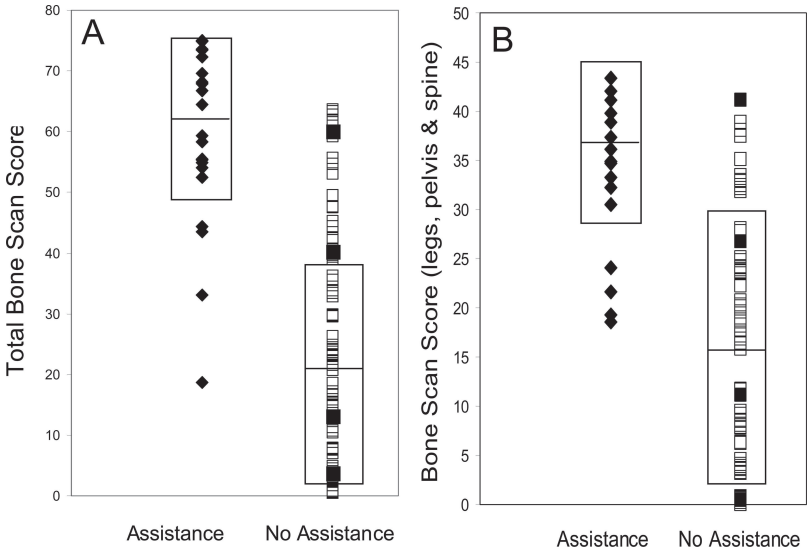

FIG. 3. Total body and regional bone scan scores in subjects with FD. (A) Total body, and (B) spine, pelvis, and lower extremity scores are shown for subjects who needed assistance with ambulation (diamonds) and those who ambulated unassisted (squares). Subjects who have not reached skeletal maturity are indicated by filled squares. Boxes with a line represent mean ± SD (Mann-Whitney U test, $p < 0.0001$ for both analyses).

TABLE 6. PROBABILITY OF NEEDING ASSISTANCE WITH AMBULATION BASED ON BONE SCAN SCORE

*Total bone scan score**	*Number of patients*	*Needs any form of assistance*	*Median age began using assistance (yr)*	*Needs a wheelchair*	*Median age began using wheelchair (yr)*
≤15	30	0 (0%)	NA	0 (0%)	NA
15.1–30	20	1 (5%)	43	0 (0%)	NA
30.1–45	19	4 (21.1%)	9 (range, 2–17)	2 (10.5%)	5 (range, 2–8)
45.1–60	16	7 (43.8%)†	7 (range, 3–27)	4 (25%)	6 (range, 3–27)
60.1–75	18	13 (72.2%)†	7 (range, 1–16)	11 (61.1%)	8 (range, 3–15)

* Bone scan scores range from 0 (no FD) to 75 (100% of the skeleton is involved).

† Because the median age patients needed ambulatory assistance was 7 yr, all patients <7 yr who were not already using an assistance device were excluded from this analysis. Five patients were excluded with a median bone scan score of 13.1 (range, 3.8–60) and a median age of 6 yr (range, 3.3–6.4 yr).

NA, not applicable.

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